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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/071,826	02/08/2002	Mitchell F. Brin	17326CIP2 (BOT)	2841

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EXAMINER	
HARRIS, ALANA M	
ART UNIT	**PAPER NUMBER**
1643	

DATE MAILED: 10/14/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/071,826	BRIN ET AL.	
	Examiner	Art Unit	
	Alana M. Harris, Ph.D.	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 July 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20,32 and 33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20,32 and 33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *04/10/02; 06/16/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of Group I (claims 1-20, 32 and 33) in the reply filed on July 14, 2005 is acknowledged.

2. Claims 1-20, 32 and 33 are pending.

Claims 21-31 have been cancelled.

Claims 11-14 and 32 have been amended.

Claims 10-20, 32 and 33 are examined on the merits.

Information Disclosure Statement

3. The information disclosure statement (IDS) filed April 10, 2002 continues not be considered in its entirety. There are several references that did not accompany the file. Reference CD and the information referred to therein has not been considered as to the merits and has been "lined through". The listing has been lined through and Applicants are invited to resubmit this document.

Specification

4. The disclosure is objected to because of the following informality: the specification does not include a brief description of the drawings. Drawings were submitted on August 27, 2004, along with the specification. However, the specification does not acknowledge these drawings. Applicants are requested to clarify whether or

not these drawings are to be considered with the specification and if so to include the proper description. See MPEP § 608.01(f). A reference to and brief description of the drawing(s) as set forth in 37 CFR 1.74.

Correction is required.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-5, 7-17, 19, 20, 32 and 33 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for treating a mammary gland disorder with *Clostridial botulinum* toxin A and *Clostridial difficile* toxin A, does not reasonably provide enablement for treating a mammary gland disorder with any Clostridial neurotoxin or preventing development of a mammary gland neoplasm/carcinoma. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The method claims read on any and all Clostridial neurotoxins including those that may not have any ability to reduce size and/or activity of mammary gland tissue. While the specification teaches the administration of botulinum toxin type A formulated as BOTOX® to mammary glands diseased by chronic cystic disease, adenosis, duct papilloma, fibroadenoma and proliferative breast disease (epithelial hyperplasia), the

specification does not teach the administration of the wide range of Clostidrial neurotoxins, such as shigella or tetanus toxins nor all the botulinum toxin types in methods of treating any and all breast diseases, including prevention, see the specification pages 45-50. Each toxin is defined by either being an endotoxin or exotoxin, reactivity with target tissue, its mode of action, heat lability, specificity and retention and release in the surrounding environment. Even when considering just the botulinum toxins one must note that *C. botulinum* produces seven antigenically distinct types of botulism toxins as noted in the specification and art known, see Johnson (Neurotoxigenic Clostridia. In: Fischetti, V.A. (EDS) Gram-Positive Pathogens. ASM Press, Washington, DC. Pages 539-550) and Hatheway (Clinical Microbiology Reviews 3(1): 66-98, January 1990). Thus the specification is only enabled for the local administration of *C. botulinum* type A and *C. difficile* toxin A neurotoxins and not any Clostridial neurotoxin. It would require undue experimentation of one skilled in the art to make and use all neurotoxins that would be possibly effective in the treatment of all breast gland disorders.

The specification fails to provide sufficient guidance to enable one of ordinary skill in the art to practice the claimed method in a manner reasonably correlated with the intended use of prevention as presented in claims 15, 20 and 35. Therefore, one of skill in the art would conclude that a prophylactic regimen would not only be unpredictable. There are no reasons why one of skill in the art would expect the claimed method would be capable of preventing a mammary disorder including breast cancer given the unpredictable nature of treating cancer. The specification fails to provide sufficient

guidance to enable one of ordinary skill in the art to make and use the variant proteins in a manner reasonably correlated with the broad scope of the claimed method. Without such guidance the specification does not support the treatment of any breast cancer/carcinoma/neoplasm in the realm of prevention. None of the examples presented in the specification supports that at the time of the claimed invention was made that Applicants were able to prevent or protect against any type of cancer. There is no guidance in the specification as to how to determine and select a population of individuals, which may or may not eventually have cancer. It is not clear what parameters would one skilled in the art use in order to identify a population of subjects that cancer could be prevented.

Thus, as supported by the scientific reasoning presented above, one of skill in the art would not expect all Clostridial neurotoxins to be effective against all mammary gland disorders with differing histological origin. Thus, one of skill in the art could not practice the broadly claimed methods, of treating mammary disorders with differing etiological features and breast neoplasms with a reasonable expectation of success.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 1, 2, 5, 6, 8, 10-14 and 33 are rejected under 35 U.S.C. 102(b) as being anticipated by Schwartz et al. (Movement Disorders 13(1): 188-190, January 1998/ IDS reference CB submitted June 16, 2003). Schwartz discloses a method of treating neuromyotonia in a muscle flap of the left breast with an injection of 300 U botulinum A toxin, see title and page 188, paragraph before "Discussion" section. This mammary gland disorder was characterized by the left breast expanding and elevating during a 24 hour period, see page 188, Case Report section, second paragraph. This disorder is considered precancerous given there was no disclosure of any cancer associated with the disorder. Moreover, it is within the purview of the Examiner that the treatment of the said disorder with the botulinum toxin A would cause about 20% - 100% reduction in the diameter of the mammary gland tissue with the subsequent reported reduction in the activity of the said tissue, see page 188, last paragraph before Discussion section.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. Claims 1, 2, 5-8, 10-14 and 33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schwartz et al. (Movement Disorders 13(1): 188-190, January 1998/ IDS reference CB submitted June 16, 2003), in view of U.S. Patent number 6,143,037 (filed June 12, 1996). The teachings of Schwartz have been presented in the 102(b)

rejection. Schwartz does not teach the claimed method wherein the administration of the botulinum toxin is carried out by implantation of a botulinum toxin implant into or onto the mammary gland.

However, U.S. Patent #6,143,037 teaches the "...targeted local delivery of pharmaceutical agents at a site of medical intervention for the treatment of ...disease", see column 1, lines 1-11. The pharmaceutical agent is a chemical compound that is therapeutic and provided in an amount effective to impart therapeutic benefit, see column 8, lines 16-26 and 34-36. It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to administer the pharmacological agent, botulinum toxin in an implant to treat a breast carcinoma/proliferative breast disease. One of ordinary skill in the art would have motivated to do so with a reasonable expectation of success by teachings in both references, that botulinum toxin A is capable of relieving breast disease symptoms and medical devices, such as implants are well known in the art for providing controlled or sustained release of pharmaceutical agents to treat disease.

11. Claims 1, 8 and 33 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 94/24155 (27 October 1994). The WO document teaches method for treating cancer (i.e. retarding tumor growth) with *Clostridium difficile* toxin A in physiologically compositions such as injectables, intravenously, as well as with solid carriers wherein these composition contain 1%-95% of the active ingredient, see page 3, lines 9-12; page 6, lines 5-28; page 7, lines 1-30.

The WO document does not teach a method for treating a mammary gland disorder with a dosage ranging between 10-3 U/kg to about 2000 U/kg carried out by and the mammary gland tissue is reduced between about 20% to about 100%, as well as the reduction in activity. However, the reference does teach the designated range in which the toxin can be administered as listed in claims 1 and 33. It would have been *prima facie* obvious at the time of the claimed invention was made to administer the *difficile* toxin A to a mammary gland disorder inclusive of a mammary neoplasm and proliferative breast disease in light of the treatment of two breast carcinoma cell lines, see page 10, Table 1. One of ordinary skill in the art would have been motivated to do in light of the teachings in the document.

The document does not teach the administration of the neurotoxin in the recited dosages. However, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to administer the Clostridial neurotoxin to a mammary gland in a variety of dosages including those designated in claims. One of ordinary skill in the art would have motivated to do so with a reasonable expectation of success by teachings well known in the art, that dosages of any pharmaceutical composition must be adjusted and optimized.

Double Patenting

12. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA

1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

13. Claims 1-20, 33 and 34 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-13 of copending Application No. 10/929,040 (filed 08/27/2004). Although the conflicting claims are not identical, they are not patentably distinct from each other because the scope of the claims is the same. The instant application's claims are directed to treating a mammary gland disorder with Clostridial botulinum neurotoxins, A-G with dosages ranging between 10-3 U/kg and about 2000U/kg. The copending application '040 has claims broadly reading on treating cancer with botulinum neurotoxins A-G with dosages ranging between 10-1Ukg and about 200 U/kg, as well as a method of treating a mammary gland cancer with the recited dosages. Even though the claims are not literally the same they both include treatment of the same type of cancer with the same agent. The broad claims of the copending application encompass breast cancer.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Alana M. Harris, Ph.D. whose telephone number is

(571) 272-0831. The examiner works a flexible schedule, however she can normally be reached between the hours of 7:30 am to 6:30 pm with alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry R. Helms can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

ALANA M. HARRIS, PH.D.
PRIMARY EXAMINER

Alana M. Harris, Ph.D.
02 October 2005